# The nature of gut microbiota in early life

## Impact

The dramatically increasing prevalence of non-communicable diseases (NCDs) such as diabetes, obesity and allergies and related economic and societal impact is a worldwide public health burden [1]. NCDs are globally the primary cause of mortality with about 60% of deaths and still numbers are steadily rising [2]. Notably, atopic diseases including allergies and asthma are the most prevalent NCDs that arise in early life [3]. Atopic diseases often have relatively moderate disease courses, but the chronicity and high prevalence pursue in a large societal and economic impact. In order to support a sustainable health care system, the primary, secondary and tertiary prevention of chronic NCD's is pivotal. These diseases are influenced by multiple environmental and genetical factors [3], and increasing evidence suggests that also the infant gut microbiota composition profoundly contribute to their etiology [5]. Although the genetic aspects of these conditions are unchangeable, the gut microbiota allows manipulation which makes it an intriguing target for new therapies to cure and prevent NCDs. Moreover, a better understanding of the natural dynamics of intestinal microbial maturation and subsequent insight into effective strategies to manipulate the microbiota could also be important for other diseases with an infectious component, i.e. necrotizing enterocolitis (NEC).

Firstly, this thesis studied the influence of host and environmental factors on early-life microbial colonization apart from the focus on a specific disease. These studies identified the neonatal subgroups with a disturbed microbiota, i.e. via caesarean birth, that might benefit most from a possible microbial treatment and could serve as a basis for personalized medicine. We further showed that the presence of methane-producing archaea in children was positively correlated with the consumption of organic yogurt and milk. Subsequently, it was confirmed that these archaea are indeed present in milk products and that dairy consumption can therefore promote the colonization of these microorganisms. Moreover, in addition to these dietary factors, bile metabolites appeared to have an important influence on the development of the small intestine microbiota of newborn mice, which was confirmed by oral administration of bile acids TCA and βTMCA. Importantly, this study was the first to show a causal role of host-derived metabolites in neonatal murine microbiota development and might have accelerated research into this area. Insight into these dietary and host factors that influence the colonization process could act as leads for future (nutritional) interventions.

Secondly, this thesis described if manipulation of the neonatal microbiota indeed can be achieved in order to improve health. We showed that the administration of probiotics, especially bifidobacteria, to preterm infants was associated with a lower risk of developing NEC, a life-threatening intestinal inflammation. Therefore, this thesis confirmed and emphasized that early childhood is a critical period in which targeted manipulation of the intestinal microbiota is possible to promote a healthy future.

Furthermore, the studies in this thesis also identified which factors influence the early development of the microbiota, and how changes in the microbiota during this life-phase relate to the onset of allergic diseases. For instance, the microbiota composition of children in two birth cohorts was investigated in relation to the development of asthma and allergies. Specific bacteria such as *Lachnobacterium* were reduced in children who subsequently developed atopic dermatitis and asthma, while a reduction in *Faecalibacterium* was indicative of atopic dermatitis. An increase in *Escherichia* was associated with an increased risk of asthma among children with pre-school wheeze. The examination of these specific bacteria is pivotal in order to both better understand the onset of these diseases and support the development of more targeted interventions. These commensal bacteria could serve as potential next-generation probiotics in the prevention of allergies or to protect against NEC, and the identified microbiota profiles of infants that did not develop such disease could be part of synthetic fecal transplants. Moreover, it also provides ways to explore new functional mechanisms in the pathogenesis of these diseases. The forthcoming interfering mechanisms, i.e. postbiotics, or the stimulation via probiotics may facilitate the development of low-cost and easy to handle treatments for affordable microbial therapies.

These non-invasive supplements to promote intestinal immune-homeostasis would contribute to improved emotional impact as well, in particular in young vulnerable infants and their parents. In addition, the identified bacteria in this thesis could also be utilized for diagnoses in the early detection of these diseases such as asthma among wheezing pre-school children. In line with this, electronic home monitoring of these bacteria might perhaps be a revolutionary scope in the future.

Alltogether, the observation that certain conditions are associated with specific changes in the intestinal microbiota composition makes it an intriguing target for new treatments, diagnoses

and personalized medicine. These findings will certainly increase the understanding of the establishing beneficial microbiota and will generate new leads for follow-up intervention studies to identify the infants that need it most and improve their gut health. Oral administration of the identified new leads (i.e. organic milk, *Faecalibacterium*, bile acids, etc.) might be a way for targeted manipulation of the gut microbiota to achieve clinical benefits, i.e. to decrease the incidence of infections by pathogens and prevent the development of immune-mediated diseases. The neonatal window may provide the best opportunity for targeted manipulation of the microbiota, potentially even with long-lasting positive health consequences which time will tell.

*Importantly, the impact of this thesis on the environment is remarkable. The thesis has only been printed for specific delegates and thereby about 50% less paper is used compared to the average common orders. Furthermore, it has been printed on ' paper' consisting of 85% to 100% of agricultural waste. The latter resulted in a reduction of 20% $CO_2$ and 47% lower eco-footprint (general environmental impact) compared to common FSC-certified paper. The improved environmental impact comprises eco-toxicity to soil and water, particulate matter, human toxicity, influence of land use, ozone layer degradation, smog formation, depletion of fossil raw materials, and acidification of soil.*

## References


1. Gouda, H.N., et al., *Burden of non-communicable diseases in sub-Saharan Africa, 1990-2017: results from the Global Burden of Disease Study 2017.* Lancet Glob Health, 2019. 7(10): p. e1375-e1387.
2. World Health Organization. *Global action plan for the prevention and control of noncommunicable diseases 2013-2020*. World Health Organization, [2013]. https://apps.who.int/iris/handle/10665/94384
3. Ogoina, D. and G.C. Onyemelukwe, *The role of infections in the emergence of non-communicable diseases (NCDs): Compelling needs for novel strategies in the developing world.* J Infect Public Health, 2009. 2(1): p. 14-29.
4. Ober, C. and T.C. Yao, *The genetics of asthma and allergic disease: a 21st century perspective.* Immunol Rev, 2011. 242(1): p. 10-30.
5. Renz, H. and C. Skevaki, *Early life microbial exposures and allergy risks: opportunities for prevention.* Nat Rev Immunol, 2020.